REMARKS/ARGUMENTS

Claims 92, 97, 98 and 100 are currently pending in the application. Support for the amendment to claim 92 is provided at e.g., p. 17, lines 5-6. Claims 101 and 102 are added. Support for claim 101 is provided at e.g., pp. 21-26 Support for claim 102 is provided at e.g., p. 17, lines 27-34, sentence bridging pp. 18, lines 24-25 and paragraph bridging pp. 97-98.

The Examiner has withdrawn the previously indicated allowability of the present claims in view of newly discovered references to Ulvestad, Selkoe, and Wong, and has rejected the claims pursuant to 35 USC 103(a) as allegedly being unpatentable over combinations of the cited references. Applicants respectfully disagree with the Examiner's conclusions, and address each of the Examiner's comments in the order made with regard to the amended claims.

1. §103(a) Rejection over the combination of Ard and Ulvestad

The Examiner has rejected claims 92, 97 and 100 as allegedly being unpatentable over Ard (*Journal of Neuroscience Research* 43:190-202 (1996); cited in previous office action) in view of Ulvestad (*Journal of Neuropathology* 53(1):27-36 (1994)). *See* p. 2 of the OA. This rejection is respectfully traversed.

Claim 92

Ard investigates the capacity of microglial cells to phagocytose Aβ. Ard hypothesizes that a lack of phagocytosis of Aβ may be related to a build up of Aβ and, hence, to the Alzheimer's pathology (see p. 190, first column, first paragraph). In this regard, Ard demonstrates that naked microglia cells can phagocytose Aβ when incubated in synthetic Aβ solutions, i.e., in the absence of any source of antibody. Such phagocytosis is of course non-Fc mediated.

Notably, when Ard adds what is purported to be antibody (fetal calf serum), Ard reports that phagocytosis is "substantially reduced." Substantially reduced, however, is actually an understatement. In four experiments, Ard essentially saw no phagocytosis whatsoever in the presence of fetal calf serum. In the only experiment in which Ard reports any significant

phagocytosis in the presence of serum, the result is an apparent artifact, which Ard never repeated.

Ard also tested microglial for capacity to accumulate Aβ from amyloid tissue sections from Alzheimer's patients. The results were characterized as a "near failure" regardless of tissue conditions, i.e., with or without antibody (p. 201, first column, third paragraph).

While the Examiner states that Ard's fetal calf serum equates to antibodies, Ard itself attributes no significance whatsoever to the presence of antibodies in the sera to microglial uptake of Aβ. Indeed, Ard never once mentions antibodies. Moreover, even if antibodies were present in Ard's sera, there is no reason to think any of the antibodies would have been reactive with Aβ or would otherwise have any role in the phagocytosis. As pointed out above, sera actually prevented the microglia from phagocytosing Aβ.

Ulvestad adds nothing to the fatally deficient Ard reference. Ulvestad investigates a possible role for microglial cells in demyelation in multiple sclerosis (see p. 27, second column, second paragraph). Ulvestad reports that microglial cells having Fcγ receptors and can phagocytose erythrocytes bound to an IgG anti-D antibody (*see* p. 29 "Phagocytosis Assay" and paragraph bridging pp. 32-33). These observations are construed as supporting a role for anti-myelin IgG mediated phagocytosis in multiple sclerosis (see p. 34, first column, second paragraph) but do not imply an analogous mechanism or any role of antibodies in Ard's experiments.

It would not have been obvious to modify the teaching of Ard to include an additional step of exposing aggregated Aβ to an antibody to Aβ or to change the timing of addition of antibody relative to addition of microglial cells for several reasons. First, Ard's goal was not to screen antibodies promoting phagocytosis but rather to investigate whether microglial-mediated phagocytosis had a role in clearing amyloid *in vivo*, failure of which might lead to Alzheimer's disease. In this regard, Ard only demonstrated that naked microglial cells could phagocytose Aβ from synthetic solutions. Except in autoimmune diseases such as multiple sclerosis discussed by Ulvestad, normal individuals do not have antibodies against their own antigens. Therefore, antibodies to Aβ or other antigens on amyloid deposits would not have been

expected to be present in undiseased individuals (or even Alzheimer's patients, given that Alzheimer's was not generally considered to be an autoimmune disease). Adding an antibody not known or likely to be present *in vivo* to Ard's assay, would have defeated Ard's purpose of assessing the potential failure of microglial cells in clearing amyloid deposits as a possible mechanism for causing Alzheimer's disease. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Second, most of Ard's results indicate sera inhibited microglial accumulation of Aβ. Insofar as the sera would have been assumed to contain antibodies (as alleged by the Examiner), and that that antibodies, had any role in Ard's experiment, the role would have appeared to be one of inhibiting Aβ accumulation. Such perceived inhibition would have taught away from adding additional antibodies to the assay. A reference teaching away from an invention is strong evidence of non-obviousness, in fact, the very antithesis of obviousness, to which a rebuttal should not even be required. *In re Buehler*, 185 USPQ 781 (CCPA 1975); *In re Hedges*, USPQ 685, 687 (Fed. Cir. 1986).

Third, although Ulvestad reports that bound antibody was necessary for phagocytosis of erythrocytes, there was no basis to conclude that such was also the case for deposits of Aβ. As discussed above, Ard reported accumulation of Aβ by microglial in the absence of any antibodies known to bind Aβ or any other antigen present on amyloid deposits. Even assuming some functional antibodies were incidentally present in the fetal bovine serum culture media used in some of the experiments, there is no reason to think that such antibodies had an appropriate specificity to bind to Aβ or any other amyloid component or otherwise influence phagocytosis. Furthermore, Ard does not even mention that antibodies are present, much less attribute any significance to them. Without any indication that antibodies had a role in Ard's experiment, it would not have been obvious to add further antibodies to the assay or alter the order of adding antibodies relative to other steps.

"A factfinder should be aware ....of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning," *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1397 (2007). Reading the teachings of the invention at issue into the prior art represents an impermissible use of hindsight. *See Ex Parte Kazumasa Ayukawa and Hiromi Matsuura* (BPAI, 2008). Here, the purported combination of references, combined in a manner that defeats the underlying purpose of one of the references (Ard), makes assumptions about a role of antibodies in Ard's experiment not taught by Ard, and ignores evidence of teaching away, does not appear to be based on the teaching of the references but rather ex post reasoning in which the disclosure of the present application is read into the reference. As in Matsuura, such is submitted to constitute impermissible hindsight reasoning.

Because there is no indication that antibodies were involved in Ard's assay and even if they were adding an antibody not present *in vivo* would defeat Ard's purpose, it was not obvious to modify Ard's teaching to use an additional or alternative antibody (i.e., an antibody to Aβ) or alter the order of adding antibody relative to other steps.

Claims 97 and 100

The Examiner acknowledges that Ard does not teach screening of monoclonal antibodies as recited in claims 97 and 100. *See* p. 3 of the OA. Ulvestad's alleged use of monoclonal antibodies to activate microglia is, however, alleged to have motivated modification of Ard to arrive at the claimed invention. *See* paragraph spanning pp. 3-4 of the OA.

The above remarks regarding lack of reason to modify Ard's experiment to use an additional or alternative antibody are equally applicable to the purported modification of Ard to use a monoclonal antibody as recited by claims 97 and 100.

Furthermore, Ulvestad does not teach use of monoclonals to activate microglia. Rather monoclonal antibodies are used to identify individual cell types derived from human CNS tissue and to identify the expression of Fc receptors on such cells. *See* p. 27, col. 2, 1st full paragraph, p. 28, col. 2, "Immunofluorescence Analysis," and p. 29, Table 1. Thus, Ulvestad discusses monoclonal antibodies only as detection reagents. Ulvestad does not discuss the use of

monoclonal antibodies in the context of inducing phagocytic activity, nor is there any indication that Ulvestad's use of monoclonal antibodies had any effect on the phagocytosis of labeled-erythrocytes. Thus, the use of monoclonal antibodies as recited in the screening methods of claims 97 and 100 would not have been obvious to the skilled artisan based on the combination of Ard and Ulvestad.

Claim 100 is distinguished on additional grounds. Claim 100 recites that the amyloid deposit is a tissue sample from the brain of an Alzheimer's disease patient or an animal having Alzheimer's pathology. Ard reported results ranged from completely negative to faintly positive, regardless of culture conditions, when microglia were cultured on tissue sections from Alzheimer's disease patient brain tissue to assess the phagocytic capability of microglia in both serum-containing and serum-free culture media (*see* p. 196, col. 2, last paragraph and p. 198, paragraph spanning columns 1-2). Ard hypothesizes that Aβ plaques in Alzheimer's disease patient brain tissue may be protected from microglial phagocytosis. *See* p. 199, col. 1, 1st paragraph. Ulvestad discusses phagocytosis of certain cells (i.e., erythrocytes), but provides no evidence that microglial can phagocytose tissue samples. *See* p. 29, "Phagocytosis Assay."

Because of Ard's largely negative results obtained with amyloid deposits from Alzheimer's patients, Ard's proposal that such deposits may be protected from microglial phagocytosis, and lack of any indication by Ulvestad that microglial cells can phagocytose tissue samples, it would not have obvious to select tissue sample deposits as a material to screen an antibody even if modification of Ard to screen an antibody were otherwise suggested, which it is not.

2. §103(a) Rejection over the combination of Ard, Ulvestad, Wong and Selkoe

The Examiner has rejected claims 92, 97, 98 and 100 as allegedly being unpatentable over Ard in view of Ulvestad as applied to claims 92, 97 and 100 above, and further in view of Wong (*Proc Natl Acad Sci USA* 82:8729-8732 (1985)) and Selkoe (US Patent No. 5,262,332). *See* p. 4 of the OA. Wong is alleged to teach that antibodies raised against the N-terminus of Aβ peptide, particularly residues 1-10, tightly bind to plaques found in Alzheimer's

disease tissue. The Examiner acknowledges that Wong does not teach binding to an epitope within residues 1-7 of Aβ, as recited in claim 98. *Id.* Selkoe is alleged to teach antibodies that bind to "about 8 or more" consecutive residues of Aβ, and argues that 7 is "about 8."

The comments regarding lack of reason to modify Ard's teaching to use a monoclonal antibody are equally applicable here.

In addition, Applicants disagree that Wong and Selkoe would have motivated selection of an antibody binding to an epitope within residues 1-7 of Aβ. As shown in Table 16 of the present application, such antibodies are particularly advantageous in clearing Aβ deposits in the claimed assays. The purported selection of Wong is not based on recognition of this or other advantage in the context of the claimed methods, but an impermissible hindsight reconstruction resulting from selective reliance on only part of the art.

Although Wong discusses an antibody binding within residues 1-10 of Aβ, he does not provide any reason to think that the antibody binds more tightly than any other antibody to Aβ, or that tight binding would be relevant to microglial mediated phagocytosis. Wong's selection of an antibody to the first ten residues of Aβ can be rationalized from the perspective that the full sequence of Aβ was not available at the time, and the first ten residues were most likely to be free from error due to amino acids being identified starting with the N-terminus. Consistent with this view, residue 11 of the partial Alzheimer's Aβ sequence shown by Wong is wrong (Gln instead of Glu). In the passage of time between Wong and the effective filing date of the present application, the full and correct sequence of Aβ became well-known and many antibodies were generated to various parts of the molecule (see, e.g., Iwatsubo, *Neuron,* 13:45-53 (1994) IDS #192 discussing C-terminal antibodies, IDS #192; and WO90/12871, IDS #85 reporting stronger staining with antibodies to a 17-24 epitope). Viewing the art in its totality, there was no reason to select Wong's antibody rather than any of the numerous other antibodies to Aβ subsequently described in the art.

Selkoe casts additional doubt on the proposition that Wong's antibody would have been selected based on its high binding affinity. Selkoe reports that antibodies raised against amyloid deposits showed stronger staining than an antibody to a synthetic peptide (see

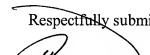
column 21, lines 13-26). Thus, if selecting an antibody with high affinity were one's goal, and one were to rely only on Wong's and Selkoe's teaching, one would presumably have selected an antibody raised against Aβ deposits rather than Wong's antibody to a synthetic peptide.

Selkoe also does not suggest replacing Wong's antibody with an antibody binding to an epitope within residues 1-7 of Aβ. A fair reading of Selkoe's comment that a fragment of about 8 or more residues can be used for generating antibodies is that a fragment of 8 residues is about the minimum size and that if a smaller fragment is used there is at least a risk of failure. There is no apparent reason in either Wong or Selkoe that the artisan would have felt compelled to test the limits of fragment size and risk possible failure in generating an antibody rather than following the protocol of Wong (who used an Aβ1-10 fragment) or Selkoe who used an Aβ1-28 fragment. Furthermore, even it the artisan had had the fortitude to test the boundaries of feasibility of fragment size, there would have been no reason for him to select an Aβ1-7 fragment, rather than an Aβ 2-8, or Aβ2-9 fragment or indeed any other seven amino acid fragment from Aβ.

For these reasons, it is respectfully submitted that the combination of Wong and Selkoe did not provide any teaching that would have led the artisan to select an antibody binding to an epitope within residues 1-7 of Aβ for use in the claimed methods.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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